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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/803,667	03/18/2004	Yasuhiro Sakai	3029-74DIV	6011

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EXAMINER	
HA, JULIE	

ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
10/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/803,667	SAKAI ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,21,24,26,28-31 and 35-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,21,24,26,28-31 and 35-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/005,753.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 28, 2008 has been entered. New claims 35-38 have been added. Claims 20-21, 24, 26, 28-31, 35-38 are pending in this application, and examined on the merits in this office action.

Withdrawn Rejection

1. Rejection of claims 20-21, 24, 26, 28-31 under 35 U.S.C. 112, first paragraph, as not enabled is hereby withdrawn in view of Applicant's persuasive arguments.

Rejection-35 U.S.C. 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

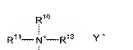
1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 20-21, 24, 26, 28-31, 35-36 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roth et al (US Patent No. 5,545,535) in view of Akai et al (US Patent No. 5,891,731) and Yue ST (US Patent No. 5,656,449).

6. Roth teaches a method of analyzing a sample thought to contain bacteria using an aqueous solution comprising one or more fluorescent dyes. The dyes stain gram-negative and gram-positive bacteria, whether live or dead (see abstract). Roth teaches that one of the dyes from a new family of unsymmetrical cyanic dyes, was unexpectedly found to label Gram-positive bacteria and Gram-negative bacteria, whether live or dead (see column 2, lines 43-46). Roth teaches that the attachment of bulkier, cyclic structures to the parent unsymmetrical cyanine dye resulted in a number of unexpected advantages for this family of dyes...although bulkier, many of the new dyes more quickly penetrate the cell membranes of a wider variety of cell types, including both

Gram-positive and Gram-negative bacteria and eukaryotic cells. Further, Roth teaches that bacteria stained with selected unsymmetrical dyes with cyclic substituents exhibit greater than tenfold more fluorescence than bacteria stained with thiazole orange (see column 3, lines 4-18). Roth teaches the same polymethine dye (11) of the instant claim 20 (see column 8, lines 45-67), where it teaches that R6 and R7 taken in combination form a fused 6 membered aromatic ring. The reference teaches that the aqueous dye solution is made by dissolving the dyes directly in water or a buffer or in an organic water-miscible solvent such as DMSO, MDF, methanol, or ethanol. Typically the dyes are dissolved in DMSO and then diluted with water or buffer or a dilute protein solution to give an aqueous dye solution where each dye is present at a concentration sufficient to five a detectable fluorescent signal when combined with bacteria (see column 16, lines 45-52), meeting the limitation of claims 35-36. DMSO is a well known reducing agent that reduces nitrite ion. Roth teaches that the bacteria sample is any sample of solid or liquid thought to contain bacteria. Typically the sample is a bodily fluids such as blood, urine, peritoneal fluid, spinal fluid or other similar fluids (see column 5, lines 15-18). The reference teaches certain amount of dye added to stain bacteria. The differences between the reference and the instant application are that the reference does not teach a cationic surfactant, wherein the cationic surfactant is quaternary ammonium salt having the formula  , the substance capable of reducing nitrite ion is mercaptoethanol, the pH range of 2.0 to 4.5.

7. Akai et al (US Patent No. 5,891,731) teaches a reagent for measuring reticulocytes and also a method of measuring them (see column 1, lines 8-10). The reference teaches a compound represented by formula (I) that is the same compound as the compound claimed in the instant application as dye (10) (see column 3, lines 45-55). The reference further teaches that the reagent for staining may also contain a cationic surfactant represented by the formula (IV) as a staining promoter (see column 8, lines 65-67 and column 9, lines 1-14). The reference teaches that the specific examples of the cationic surfactant are decyltrimethylammonium bromide (see column 9, lines 15-19). Furthermore, the reference teaches that the concentration of the cationic surfactant which is a staining promoter, the effective concentration may be 300-20,000 mg/liter (see column 9, lines 19-23). The reference teaches certain amount of dye added to stain bacteria (see Tables and Examples). Akai further teaches that the buffer is used to keep the pH constant, such as carboxylates, phosphates, Good's buffer, taurine, triethanolamine (see column 8). The reference teaches that as the polyvalent anion, sulfate ion, phosphate ion, carbonate ion, and polycarboxylate ion…citric acid, sulfuric acid, phosphoric acid, EDTA and alkali metal salts (see column 8, lines 13-17).

8. Yue reference teaches preparation and use of fluorescent stains for nucleic acids derived from neutral unsymmetrical cyanine dyes comprising a substituted benzazolium ring system linked to a methine bridge to a pyridine or quinoline ring system. The reference teaches that the dyes have greater stability in buffered solutions than in water alone; and agents that reduce the levels of oxygen radicals, such as β-mercaptoethanol, contribute to the stability of the dyes (see column 6, lines 18-21). Additionally, the

reference teaches that the dye stains prokaryotes, particularly bacteria, including both Gram-negative and Gram-positive bacteria, as well as yeast and other fungi, and spores (see column 8, lines 9-15).

9. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Roth et al and Akai et al, since they both teach staining of cells using polymethine dyes. One of ordinary skill in the art would have been motivated to add the cationic surfactant that is quaternary ammonium salt, since it promotes staining. Furthermore, one of ordinary skill in the art would have been motivated to add in β-mercaptoethanol, since it is commercially available and it enhances stability of the dyes. There is a reasonable expectation of success, since the references teach that polymethine dye can stain bacteria and other components found in urine and blood and other biological fluids, and one would expect that adding cationic surfactant (ammonium salts) and agent that reduces nitrite ions would enhance the stability of the dye and promote the staining of the cell.

In regards to the optimization of the pH, the amount of the dye added, and the cationic surfactant added to the assay sample, the MPEP states the following: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. *"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)* (Claimed process which was performed at a temperature between 40°C and 80°C

and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("*The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.*"); *In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969)* (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Therefore, the amount of dye added and cationic surfactant added to the reagent, and the pH of the buffer is deemed merely a matter of judicious selection and routine optimization that is well within the purview of skilled artisan.

10. Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Roth et al (US Patent No. 5,545,535) in view of Akai et al (US Patent No. 5,891,731) and Yue ST (US Patent No. 5,656,449) as applied to claims 20-21, 24, 26, 28-31, 35-36 and 38 above, and further in view of Inoue J (US Patent No. 5,891,733).

11. The teachings of Roth, Akai and Yue patents are described, supra. The difference between the references and the instant claim is that the reference does not teach ethylene glycol.

12. However, Inoue patent teaches a reagent for analyzing solid components in urine and a method for analyzing solid components in urine. The solid components in the urine are analyzed by flow cytometry (see column 1, lines 9-14). The reference teaches that examples of solid components include erythrocytes, leukocytes, epithelial cells, urinary casts, bacteria, fungi, crystals and mucus thread. Analyzing these components in urine is of great importance for early discovery of renal and urinary diseases (see column 1, lines 19-23). Inoue reference teaches NK-2782 that is the same dye that is claimed in instant application as dye (2) (see column 7, lines 1-6 and 35-40). Additionally, Inoue teaches that the reagent consists of two solutions, a dyeing solution and a diluent solution, stability in preserving the dyeing solution can be improved by dissolving the dyes into a water soluble organic solvent, because dyes are often unstable in an aqueous solution...A water soluble organic solvent that can be used in this case is preferably, methanol, ethanol, n-propanol, ethylene glycol....Considering the influence on cells in urine and the viscosity, ethylene glycol is the most preferable (see column 10, lines 60-67 and column 11, lines 1-8).

13. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of the prior arts since the prior arts teach the staining of bacteria and components of bodily fluids (urine, blood and such). One of ordinary skill in the art would have been motivated to add in ethylene glycol to the staining reagent, since

Inoue teaches ethylene glycol is a stabilizing agent preserving the dyeing solution. Additionally, Inoue teaches that ethylene glycol is preferred for urine, due to the cells and viscosity of the urine. There is a reasonable expectation of success, since the polymethine dyes are used to stain bodily fluids for measuring such things are bacteria, leukocytes, erythrocytes, reticulocytes, fungi etc, one would expect adding the components that would promote staining and stabilize the dyeing solution, would enhance the staining of bacteria in the urine and other bodily fluids.

Obviousness Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

15. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

16. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 20-21, 26 and 38 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 and 8 of U.S. Patent No. 7,422,870 in view of U.S Patent No. 5,656,449.

18. The instant claims are drawn to a method of preparing an assay sample for detecting bacteria by a flow cytometry comprising providing a diluent comprising a cationic surfactant, a buffer for maintaining a pH or 2.0-4.5, an effective amount of a substance capable of reducing nitrite ions and a staining solution comprising a polymethine dye for staining bacteria, mixing a urine sample with the diluent.

19. Claims 1-4 and 8 of U.S. Patent No. '870 are drawn to a method for counting bacteria in a clinical specimen that comprises Gram positive and Gram negative bacteria, the method comprising: preparing a first assay sample by dividing the clinical specimen into at least two parts and staining a first specimen part using a fluorescent dye, wherein the said fluorescent dye comprises a polymethine dye, a cationic surface-active agent (cationic surfactant), and the staining is performed at a pH of between about 2.5 and about 4.5 (see claims 1-4). Claim 8 is drawn to utilizing flow cytometry. The difference between the copending application and the instant application is that the reference does not teach a substance capable of reducing nitrite ions.

20. However, U.S. Patent No. 5,656,449 teaches cell types for which the dye is an effective nucleic acid stain include cells with or without nuclei, including both Gram-negative and Gram-positive bacteria, as well as yeast and other fungi and spores (see column 8, lines 9-15). Furthermore, U.S. Patent '449 teaches that the dyes have greater stability in buffered solutions than in water alone; and agents that reduce the levels of

oxygen radicals, such as β-mercaptoethanol, contribute to the stability of the dyes (see column 6, lines 18-21).

21. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of U.S. Patent '870 and '449, because both teach fluorescently staining bacteria with polymethine dyes. One of ordinary skill in the art would have been motivated to add in the nitrite ion reducing agent, such as β-mercaptoethanol, since Patent No. '449 teaches that these agents contribute to the stability of the dyes. There is a reasonable expectation of success, since adding the nitrite ion reducing agent would at least enhance the stability of the dyes thereby, making the staining of the bacteria more stable.

Conclusion

22. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anish Gupta/
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